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Bindarit reduces uMCP-1 in lupus nephritis patients

Preclinical and clinical evidence has amassed to indicate a role for monocyte chemoattractant protein-1 (MCP-1) in kidney injury. It has been shown that MCP-1 gene and protein expression is upregulated following protein overload in renal tubular cells. In addition, urinary MCP-1 (uMCP-1) is proportional to the degree of albuminuria. Bindarit, an indazolic derivative, has been shown to be an inhibitor of MCP-1 production in vitro and in vivo. Findings from a double-blind, placebo-controlled, pilot study of bindarit in patients (Caucasian, n = 22, 19 to 50 years of age, both genders) with active lupus nephritis (WHO classes III to IV), receiving standard methylprednisolone treatment, were presented by Angelina Research Center's Angelo Guglielmotti. Methylprednisolone (1 g iv, alternate days) was administered to patients in the first week of study. In weeks 2 to 24, patients received bindarit (600 mg bid; n = 11) or placebo (n = 11) and oral methylprednisolone (gradually reduced from 40 to 4 mg/day). Primary endpoints were disease remission and time to relapse according to the European Consensus Lupus Activity Measurement (ECLAM) index; secondary endpoints were uMCP-1 and urinary albumin excretion (UAE). At week 8, uMCP-1 was reduced by 29% for bindarit-treated patients; at week 19, the maximum reduction relative to baseline was attained (62%). Relative to baseline, bindarit reduced UAE by 71% at week 24 and uMCP-1 reduction correlated with this. From these results it was suggested that MCP-1 may be a potential therapeutic target for kidney disease and that further clinical trials are merited to investigate bindarit's therapeutic potential.

YM-254890 suppresses airway responses in rodents

YM-254890, a selective depsipeptide, is a selective Galpha (q/11) inhibitor. In previous studies, carotid patency status post-thrombolysis was significantly improved by intravenous bolus injection (10 microg/kg); however, systemic blood pressure was decreased in anesthetized rats by 30 microg/kg of the compound. Furthermore, bleeding time was prolonged and systemic blood pressure was decreased in mouse models at three-fold the dose required to produce significant effects on neointima formation and thrombosis. Susumu Tsujimoto (Astellas Pharma) presented findings from studies in spasmogen-induced bronchoconstriction and cigarette smoke (CS)-induced airway inflammation rodent models, which suggested that local administration of YM-254890 may be effective in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Methacholine (MCh)-induced bronchoconstriction in rats was dose-dependently suppressed by intratracheally administered YM-254890 (ED50 = 0.73 microg/kg). There was no effect on systemic blood pressure or bleeding time at doses of up to 30 microg/kg. Relative to the saline control, MCh-induced bronchoconstriction was significantly inhibited by YM-254890 for 6 h following intratracheal administration. When administered by metered-dose inhalation (0.1%, 1 puff), the compound significantly inhibited MCh-induced bronchoconstriction in rats (30 min post-inhalation). In a leukotriene D4-induced guinea pig model of bronchoconstriction, the compound had an ED50 value of 1.1 microg/kg. In mice experiencing CS-induced airway inflammation, infiltration of neutrophils, eosinophils and lymphocytes in to the airways was significantly suppressed by the intranasal instillation of YM-254890 (10 microg/kg). Furthermore, histological examination of lungs from rats demonstrated that treatment with the compound (0.1%, 3 puffs qd for 7 days) induced alveolar foam cells and inflammatory cells.

Pulmonary monocytic inflammation reduced by INCB-3344

Chronic inflammation of the lung is a principal pathology in patients with COPD. In induced sputum and bronchial biopsies of these patients, macrophages, neutrophils and CD8+ lymphocytes are predominantly elevated. MCP-1, which is known to act via chemokine (C-C motif) receptor 2 (CCR2), has also been shown to be elevated. Boehringer Ingelheim's Silke Hobbie presented data from a study investigating the effect of INCB-3344, a CCR2 antagonist, in two mouse COPD models of pulmonary monocytic inflammation. MCP-1-induced pulmonary monocytic inflammation was completely suppressed by INCB-3344 (ID50 = 22 mg/kg). At 100 mg/kg, the compound reduced CS-induced pulmonary monocytic inflammation by 47% which was comparable to the phosphodiesterase4 (PDE4) inhibitor roflumilast (Daxas; Nycomed) which reduced CS-induced monocytic inflammation in mice by 34% when administered at a human relevant dose of 5 mg/kg. Therefore, it was proposed that CCR2 inhibition may provide an anti-inflammatory therapeutic option for COPD patients.

CXCR7 has a pathogenic role in RA

In rheumatoid arthritis (RA), it is known that interactions between CXCL12 and CXCR4 in the synovium play an important part in the production of inflammatory cytokines, angiogenesis and inflammatory cell recruitment. CXCR7 has recently been determined to be an alternative receptor for CXCL12; it is thought that tumor growth and homing of renal progenitor cells may be promoted by the interaction between these two components. Kaori Watanabe (Tokyo Medical and Dental University) presented findings from a study performed in collaboration with ChemoCentryx, determining the potential pathogenic role of the CXCL12/CXCR7 pathway in RA. In RA synovium, CXCR7 was expressed on endothelial cells; this expression was much weaker in osteoarthritis synovium. In unstimulated human umbilical vein endothelial cells (HUVECs), CXCR7 mRNA was detected and was upregulated by IL-beta stimulation. In IL-beta-stimulated HUVECs, CXCL12 increased CXCR7 expression which was not changed with stimulation by CXCL12 or TNF-alpha alone; stimulation with IL-beta alone downregulated CXCR4 mRNA. CXCL12-induced tube formation was inhibited by the CXCCR7 antagonist CCX-733 and the CXCR4 antagonist plerixafor (Mozobil); this also occurred for IL-beta-enhanced CXCL12-induced tube formation. In murine collagen-induced arthritis (CIA), treatment with 10 mg/kg CCX-733 decreased soft tissue swelling scores and significantly lowered destructive changes in bone. Furthermore, the compound had no effect on anticollagen antibody levels. These results suggest that CXCR7 may also have a function in angiogenesis in RA synovium. Therefore, given its role in angiogenesis, CXCR7 may be a potential therapeutic target for RA.

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